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INTRATHORACIC METALLIC FOREIGN BODIES

A Review of the Literature

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During World War II many problems of thoracic injury have been clarified, and some new ideas have been introduced. Numerous papers have appeared in the literature on the proper handling of battle injuries of the thorax, at the forward hospitals (Field and Evacuation hospitals) in the General Hospitals of the Zone of Communications, and General Hospitals in the Zone of the Interior (United States). Certain apparent differences of opinion in regard to the handling of retained intrathoracic foreign bodies have appeared in the literature. These differences of viewpoint seem to exist between surgeons in different echelons; but there is essential agreement between surgeons in the same echelon. The interest in this subject began with the patients with thoracic injury which were treated in a forward Evacuation Hospital during the Italian campaign. It was always difficult to follow cases after they left the Army Sector and entered base hospitals. During periods when large numbers of battle casualties were being treated, it was quite impossible to follow them. Many patients left the forward hospitals carrying intrathoracic foreign bodies. The fate of these patients has stimulated interest in this subject.

According to Carter and DeBakey,[6] in the American Civil War of each 10 wounds, 9 were due to bullets, and 1 to high explosive shell fragments. In World War II, the figures were almost reversed —2 out of 10 wounds were due to bullets and 8 were due to high explosive shell fragments. Of all retained foreign bodies, a little

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over 10 per cent are bullets, the remainder high explosive shell fragments. This proportion is not borne out in other reports, bullet wounds usually constituting a much smaller percentage. Shell fragment wounds account for a greater total in morbidity and mortality than bullet wounds because of their greater frequency and because of the greater damage done by the irregular object. Shell fragments are more likely to carry extraneous material into the tissues, hence result in a greater percentage of infected wounds.

In Field and Evacuation hospitals in Italy, the treatment of chest injuries was directed primarily at the conservation of life and the prevention of infection. This resolves into the treatment of shock with adequate blood replacement, and the restoration of normal cardio-respiratory physiology. In many cases it was necessary to carry on these phases together. When the patient had sustained multiple wounds, it was essential to reestablish normal, or as near normal cardio-respiratory function as possible, before the other wounds could be treated, fractures reduced, or the abdomen explored. This might result in a dilemma in a patient who required abdominal exploration, but who also needed additional time for his cardio-respiratory system to become stabilized. It is axiomatic that patients with chest injuries alone do not often die of infection but frequently do die of mechanical difficulties.

In the shock wards, patients could be given blood transfusions, oxygen, have the chest aspirated, or an intercostal catheter could be inserted for tension pneumothorax. Intercostal nerves could be injected for the relief of pain, to facilitate cough and thus obviate the danger of atelectasis in a patient with already reduced vital capacity as a result of his injury. Sucking wounds were closed by a tight occlusive dressing until the patient's improved general condition made operative closure possible with a minimum of risk.

A complete debridement of the chest wall wound in some instances involved the opening of the pleural space, or required the inspection, cleansing, and closure of an already lacerated and open parietal pleura. A prolonged search for foreign bodies was not indicated, and only those foreign bodies which could be easily removed were so treated.

Operations other than simple debridement were done in forward hospitals (Field and Evacuation) when there was evidence of gross continued bleeding, uncontrolled broncho-pleural fistulæ, evidence of transdiaphragmatic or esophageal injury. Only one case of cardiac injury was encountered, in a patient admitted 24 hours after injury by a single shell fragment, which had penetrated the left chest wall, left lower lobe of the lung, diaphragm, kidney, spleen,

stomach, pericardium, inferior vena cava, right auricle, and right pulmonary hilar region. This patient died after a lengthy repair of the injuries.

These indications for surgical treatment other than debridement are essentially the same as those listed by Elkin[12] who states that the principal considerations in the primary treatment of chest wounds are: (1) the treatment of shock, (2) the restoration of normal cardio-respiratory physiology, and (3) the treatment of complications or sequelæ. Most patients in forward hospitals were not held sufficiently long for evidence of infection to develop. A detailed discussion of treatment of chest injuries in a forward hospital is given by Betts and Lees.[1]

In a discussion of the management of intrathoracic and thoracoabdominal wounds in the combat zone, Snyder[24] recommends that, when not contraindicated, rib fragments and foreign bodies of more than 2 cm. in diameter may be removed in forward hospitals. Large intrapulmonary foreign bodies should be removed when feasible, especially when extensive lung damage is present. He feels also that all right-sided thoracoabdominal injuries should be explored because of the danger of hemorrhage and bile empyema, as well as all left-sided ones. Some other authors, Welch,[26] for example, have recommended aspiration only for right-sided transdiaphragmatic injuries, when the roentgenogram shows only a small intrahepatic foreign body.

In general, the majority of thoracic wounds seen in forward hospitals recovered satisfactorily on a system of replacement of blood loss, debridement and closure of chest wall wounds, aspiration of blood and air from the pleural space, insertion of an intercostal catheter for tension pneumothorax, and novocaine intercostal block for fractured ribs. A serious attempt was always made to aspirate the pleural space as completely as possible before evacuating the patient back to the base hospitals. It was the consensus that air replacement was not advisable. If fractured ribs were a part of the injury, intercostal nerve block was much more effective for the relief of pain than morphia, and lasted much longer. Complete aspiration of blood from the pleural space prevents much future infection, and avoids operations for decortication in clotted hemothorax. Many factors play a part in the development, or failure of development, of infection. The terrain in which the fighting occurred, temperature, moisture, type of soil, delay from injury to definitive treatment, and early use of chemotherapy are all important.

The experimental work of Daniel[10] is of interest and importance

in the conservative treatment of thoracic injuries. It indicates how injury to the lung occurs even when the missile has not penetrated the lung or pleura. Daniel fired bullets of varying weights and muzzle velocities at different distances into the chests of dogs, and carefully studied the effects, which he summarizes as follows:

> A shock wave which may be comparable to air and water borne blast waves may be transmitted through the tissues of the chest wall and the lungs. Transmission of this wave of compression or blast takes place in the solid or "fluid" tissues of the chest wall without evidence of damage to these tissues which do not lie in the path of the bullet, and injure the underlying, air containing tissue of the lung. Rupture of the walls of the alveoli and extravasation of blood into the air spaces were consistently observed in these animals. The extent of injury and amount of hemorrhage varied greatly under different conditions. The direction of the bullet is of great importance in determining the extent of damage which is inflicted upon the parenchyma of the lung. The degree of pulmonary injury found in tangential wounds of the chest appears to be directly related to muzzle energy, calculated by the weight and muzzle velocity of the bullet. The rupture of alveolar walls and bleeding in air spaces of the lung was much more widespread and profuse when the bullet traversed the chest wall tangentially than when it coursed directly through the parenchyma of the lung. This is true whether or not a superficial wound of the lung is created.

West[27] reports a high mortality for operative treatment of chest wounds in battle casualties. There were 10 deaths in 30 cases. Of 3 cases with tension pneumothorax, one died, and there were 12 deaths in 36 operations for thoracoabdominal injuries.

Holman[16] advocated aspiration when indicated for pressure. He also reported several cases of late empyema from retained foreign bodies and empyema following inadequate debridement of wounds of entrance and exit. He suggests the necessity of evacuation of blood clots from the pleura and decortication when the lung fails to reexpand after traumatic hemothorax.

Since most patients in forward hospitals did not require open thoracotomy, many were sent to the base hospitals with the foreign body still in the thorax.

The conditions presented to the thoracic surgeons in the Base Hospital Chest Centers were quite different from those seen in the forward hospitals. Many patients required only convalescence and observation. Those with complications and with large retained foreign bodies often presented problems of major difficulty.

In the Mediterranean Theater of Operations, the surgical consultant, Colonel E. D. Churchill[7,8] established policies for the handling of battle casualties. Foreign bodies in the pleura or lung over a size arbitrarily set at 1.5 cm. in greatest diameter were to be removed in the thoracic surgical center in the base (General) hospital. Operations were indicated for prevention of infection, or

for the removal of clotted blood from the pleural space. This was often done at the time of the removal of the foreign body.

The removal of clotted blood and decortication, if necessary, is well discussed by Burford[4] and Samson.[23] Failure of the lung to reexpand progressively and quickly, within four weeks of adequate drainage, was accepted as an important indication for thoracotomy and decortication.

Unquestionably, foreign bodies causing symptoms should be removed as soon as expedient. It may have been impossible to remove the foreign body in the forward hospital because of the patient's condition. For several months, Samson[23] removed foreign bodies of 8 mm. or over from pleural cavity, lungs, mediastinum and myocardium. Later a minimum size of 1.5 cm. was used as the criterion for removal of asymptomatic foreign bodies. After 3 to 4 weeks, thoracotomy was reported to be more difficult due to fibrosis around the intrapulmonary foreign body. Pleural adhesions may increase the difficulty of palpating the foreign body in the lung. Samson prefers to operate between 4 to 10 days after injury, but some cases were done as long as 25 days after injury. This delay allows time for secondary closure of wounds of the chest wall, permits reaeration of alveoli, and absorption of interstitial fluid, the reestablishment of complete tracheal and bronchial patency, and at least partial absorption of extravasated intrapulmonary blood. Tuttle[25] reports that operation for the removal of intrathoracic foreign bodies less than 3 weeks after injury resulted in unfavorable results in 31 per cent of cases. When the operation was delayed to a period after 3 weeks, the percentage of unfavorable results fell to 3 per cent.

Samson comments thus, "The validity of removing asymptomatic shell fragments as a prophylactic procedure cannot be decided in a theater of operations. The final answer must come several years hence from a determination of morbidity rates following operation, as compared to the percentage of complications which develop in patients with retained shell fragments." Harken,[15] in a review of the work of Chest Surgical Centers in England, states that 15 per cent of the patients admitted to these chest hospitals had retained intrathoracic foreign bodies. Of these 8 per cent required removal. In Harken's hospital 982 patients with chest injuries were admitted. The removal of foreign bodies was done in 247 patients, using the measurement of 1.5 cm. as a minimum criterion, as well as symptoms referable to the missile. According to Harken, foreign bodies were removed to prevent hemorrhage and suppurative processes. Other factors considered were size and irregularity, proximity to major vessels and bronchi, and dependent position in the paren-

chyma, and the surrounding reaction as determined clinically and by means of the roentgenogram. The distribution of foreign bodies was recorded as follows: lung 162, mediastinum 32, heart and great vessels 16, diaphragm 10, subdiaphragmatic space 14, pleura 31.

The attitude of British surgeons in a similar echelon, Chest Centers in Overseas General Hospitals, is quite like those of the Americans. D'Abreu[9] reporting in two articles states that foreign bodies of 1 cm. or more in diameter were removed.

In D'Abreu's series, of 260 penetrating wounds of the thorax, 84 had retained foreign bodies distributed as follows: lung 55, pleura 15, mediastinum 14. There were 15 deaths out of the total of 260 chest cases, 11 of which occurred more than a month after wounding. Of 16 lung abscesses, 9 surrounded metallic foreign bodies or indriven rib fragments; 7 of these 9 cases had small abscesses and were diagnosed radiographically or by finding pus at operation. None of them were comparable to the typical putrid lung abscess of civilian practice. The patients showed no gross symptoms and all recovered after operation, which was directed at the removal of the foreign body and not against the suppurative process. The remaining 2 patients died of secondary hemorrhage. In one case from a pulmonary vessel, and the other from a septic erosion of the descending aorta which formed the inner boundary of an abscess cavity which was mainly in lung tissue. Both were too ill for the removal of the missile.

Of the 260 cases, 77 had empyemata. Of the pulmonary foreign bodies, 80 per cent were comparatively superficial in the lung. Only 3 of the missiles were bullets; one in the lung, one in the pleura, one in the pericardium. All other foreign bodies were fragments, from shell, bomb, mortar or grenade.

Tuttle[25] et al, during the African and Sicilian campaigns, removed foreign bodies of 7 mm. size or over. In Italy, in accordance with the Theater policy, they removed foreign bodies of 1.5 cm. diameter or over. No cases of lung abscess were noted.

The following figures from Parker[22] and Burford's work indicate some of the reasons for operating on patients overseas who had retained metallic foreign bodies. Of the 291 cases with intrathoracic foreign bodies, 75 had serious complications, as follows:

Empyema	45
Lung abscess	4
Delayed or recurring hemoptysis	4
Secondary intrapleural hemorrhage from lung	2
Late or recurrent bronchopleural fistula	18
Mediastinal abscess	2
Total	75

Complications of the operation for removal of intrathoracic foreign bodies followed nearly 10 per cent of the operated cases and consisted of the following:

Empyema with wound infection	3
Empyema without wound infection	1
Clotted hemothorax	1
Femoral thrombophlebitis	1
Atelectasis	1
Secondary hemorrhage from lung	1
Bronchopleural fistula	2
Total	10

9.8 per cent of 102 cases

Table I illustrated the number of cases seen and operated upon by several overseas chest centers. The reported mortality is quite low. These figures do not include foreign bodies of the heart and great vessels, but do include those foreign bodies found in the mediastinum.

The figures reported by Nicholson and Scadding[20] recorded the experience of a British General Hospital during the desert fighting across North Africa.

The function of overseas Field, Evacuation and General Hospitals is the conservation of life and limb and the prompt restoration to duty of as many soldiers as possible. Patients were returned to the United States (Zone of the Interior) when it was evident that their return to duty was a mater of 3 o 4 months or longer. Consequently, few patients were returned to the Zone of the Interior solely because of retained intrathoracic foreign bodies. Therefore, the patients who exhibited these metallic objects usually had few complaints referable to them, and were usually returned for other reasons. Those patients whose intrathoracic foreign bodies produced symptoms and most of those whose roentgenogram showed large foreign bodies (over 1.5 cm.) were operated upon in the Overseas Chest Centers.

It could be predicted that the experience of thoracic surgeons in chest centers in the United States would be quite different from that of the overseas surgeons. Without the urgent necessity to return men to duty to combat units, the attitude and approach to the problem by surgeons in the Zone of the Interior was likely to be more conservative than that of more forward chest surgeons.

The experience gained in World War I led to the belief that retained foreign bodies of small size (probably not exceeding 2 cm.

in diameter) should be left alone, and that operation was indicated only for larger foreign bodies. The British observed that "Rifle bullets and small pieces of shell retained in lung or pleural cavity in noninfected cases rarely cause any disability, and their presence did not delay the return of the soldier to full duty. These should be left alone unless they give rise to a continuance of such symptoms as pain, cough, dyspnea, expectoration or hemoptysis." (Gask, 1922.[14])

Tudor Edwards[11] condemns the removal of intrathoracic foreign bodies in forward hospitals, and states that wounds heal well in the presence of foreign bodies not associated with infection. However, he points out that complications may occur as late as 20 years after wounding due to the retention of large intrathoracic foreign bodies. When no sepsis is present, the optimum time for removal of large foreign bodies is the fifth or sixth week. Edwards quotes Konjetzny and Sauerbruch who in 1939 and 1941 strongly recommended the removal of all irregular foreign bodies from the lung in order to prevent secondary lung changes. After secondary pulmonary changes have occurred, Sauerbruch reported 3 fatalities in 45 operated cases and Konjetzny reported 1 death in 37 cases operated upon for removal of intrapulmonary foreign bodies. Edwards feels that all pericardial foreign bodies should be removed.

The experience of Paine[21] in a general hospital in North Africa is more nearly that of the Z. I. chest centers than that of the more forward chest centers. He reports that of 81 cases of intrathoracic disease and injury, 66 battle casualties had retained foreign bodies. It was not deemed necessary to operate on any of these. None of these patients presented any complications and none had symptoms referable to the foreign bodies. Most of the metallic objects were small, 1 to 10 mm. in greatest diameter. Two or 3 cases varied from 10 to 15 mm. Of the total 81 cases, 25 per cent returned to duty.

Blades,[2] reporting from the chest center at Walter Reed Hospital, points out that there is no accepted rule to follow in determining which metallic foreign body should be removed and which should not. The optimum time for removal has not been established. He suggests the individualization of all cases and considers the following points:

(1) Whether the foreign body produces signs or symptoms,

(2) The size and position of the fragment,

(3) The psychosomatic effect on the patient who knows he has a shell fragment in his lung. Of the symptoms, pain, dyspnea, and hemoptysis are the most frequent. Pain and dyspnea are particularly difficult to evaluate when

TABLE I

	Parker-Burford American	Tuttle et al American	Paine-Plankers American	D'Abreu et al British	Nicholson-Scadding British	Harken American
Total No. Cases of Intrathoracic Wounds	1058	320	81	264	291	982
Total No. Cases with Retained Foreign Bodies	291	68	26	92	216	?
No. Cases Operated for Removal of Foreign Bodies	102	44	0	50	28	215
Deaths	0	?	—	2	?	1

Parker-Burford—1.5 cm. diameter criterion for removal

Tuttle—.7 cm. diameter criterion for removal, later 1.5 cm.

Nicholson-Scadding—1 cm. criterion for removal

D'Abreu—1 cm. criterion for removal

Harken—1.5 cm. criterion for removal

All figures excluded heart and pericardium.

psychosomatic reactions are a probable factor in the patient's complaints. Blades advocates the removal of all large foreign bodies.

Thirty cases with foreign bodies were reported. Sixteen of them had operations for removal. There were no deaths. The 14 remaining patients had small, often multiple, foreign bodies and no symptoms.

Kay,[17] of the Percy Jones General Hospital, Thoracic Surgical Center, in discussing Blades' paper, stated that if foreign bodies cannot be safely removed at the time of the original debridement and thoracotomy, then 3 to 4 months should elapse before attempting their removal, and then only if definite indications exist. Most foreign bodies when small and in the periphery of the lung are harmless. A number of cases have been seen in which the foreign body was removed 4 to 6 weeks after the original injury. Many of these patients developed bronchopleural fistulæ and empyemata.

Meade,[18] of the Kennedy General Hospital, Thoracic Surgical Center, also in discussing Blades' paper, reported that none of the patients seen at that center with retained foreign bodies have had any symptoms from the fragments and no intrathoracic foreign bodies have been removed. One patient had a small foreign body in the ventricular wall, not producing symptoms, and it was thought inadvisable to interfere.

Garland,[13] in citing the experience in a naval hospital, reports that during a period of 3 years, x-ray examinations had been made on more than 150 men with intrathoracic foreign bodies from 1 to 12 months following injury. Most were seen in the period of 3 to 5 months following wounding and several were followed 3 additional months. Fragments varied from 1 to 40 mm. in length and 1 to 30 mm. in diameter. Approximately 25 per cent had fragments of 1 cm. or over. About 20 per cent had associated bone injuries, usually rib fractures, 75 per cent showed pleural changes, 15 per cent showed pulmonary changes in ordinary roentgenograms. Most of the foreign bodies were shell fragments. There were no cases of hemoptysis, 10 per cent had mild symptoms, 10 per cent had moderately severe symptoms, and there were virtually no symptoms in the remaining 80 per cent. He reported several cases of symptomless intrapulmonary foreign bodies measuring 3 cm. in diameter, and whose x-ray films showed little or no scarring in the region of the metallic object.

The following table is of interest since it lists the typical experience of the general hospitals in the Zone of the Interior.

TABLE II

AMERICAN GENERAL HOSPITALS IN THE UNITED STATES

	Blades Dugan	Garland
Total No. Cases with Retained Foreign Bodies	30	more than 150
No. Cases of Removal of Foreign Bodies	16	10
Mortality	0	0

The localization of intrathoracic foreign bodies is not properly part of this problem. Moorhead,[19] in discussing the removal of metallic foreign bodies with an electromagnetic locater, observes that in deciding to remove a metallic object, factors of scar following operation, the dangers of the foreign body in respect to immediate and late tissue damage, the patient's fear of the foreign body, and legal and compensation case aspects, should all be carefully considered. The possibility of migration of the foreign body is important, especially in intrathoracic cases. Smooth cylindrical objects such as bullets tend to migrate more than rough irregular shell fragments. Many civilians are quite unconscious of carrying around tool fragments, bullets or multiple buckshot. "The travels of needles as recounted by some newspapers and magazines are usually far more romantic than anatomic."

Brailsford,[3] a British radiologist, states: "I have seen many fragments and bullets over this size (½ inch in diameter) in the lungs of pensioners from the last war without any symptoms or radiographic indications for removal. I have also seen patients in this war with such foreign bodies who were symptom-free and showed no radiographic evidence of reaction around the foreign body, but who developed symptoms and radiographic signs after surgical removal. Size alone is a difficult guide to removal, each case must be assessed on its own merits." He quotes no figures to substantiate his impressions.

The foreign body localizers issued for use in the forward hospitals in Italy were modeled on the minesweeper equipment of the engineers. The localizers were not very satisfactory, and were not extensively used.

In determining the exact position of an intrapulmonary foreign body, a bronchogram may be of considerable aid in designating the segment of the lung involved.

Burbank, Burford and Samson[4] suggest dividing the anterior-posterior and the lateral x-ray films into three fairly equal zones. These are then labeled A, B, C, and A′, B′, C′ which may be of aid in locating the foreign body with respect to the chest wall and the depth in the lung.

There is apparently uniform agreement that metallic foreign bodies in and about the heart and pericardium should be removed if operation seems feasible. In general this applies also to mediastinal foreign bodies because of the danger of erosion of important structures.

Intrapulmonary foreign bodies, if small and multiple, should not be removed according to the evidence presented. Very large foreign bodies probably should be excised in spite of occasional reports of large silent fragments. Irregular, jagged objects tend to cause more damage to chest wall, ribs, and lung than smooth bullets. The former tend to carry in clothing and other extraneous material, hence are more likely to result in an infected wound, empyema, or lung abscess.

The lung apparently tolerates rather well sterile metallic foreign bodies, but not those associated with infection nor those consisting of cement, bone, clothing or other organic material.

The late symptoms of foreign bodies consist of:

(1) Symptoms produced by migration
(2) Erosion of vessels or bronchi
(3) Recurrent infection (including late pulmonary suppuration)
(4) Pleural irritation
(5) Nerve pressure
(6) Changes in adjacent structures, due to original injury, or to presence of the foreign body

On the basis of patients observed who carried intrathoracic foreign bodies from World War I for many years without apparent ill effects, it seems wise to recommend that silent foreign bodies of less than 2 cm. be not disturbed. Most authors feel that large foreign bodies (probably 2 to 3 cm. and over) should be removed on the basis of possible late complications. Some complications have been reported as late as 20 years after injury. It hardly seems necessary to mention that in measuring foreign bodies on the x-ray

film, objects will vary in size depending on the position of the foreign body in relation to the x-ray tube and film.

In veterans who present themselves for consideration of removal of intrathoracic foreign bodies, careful study will be necessary to determine whether the symptoms presented are actually due to the physical presence of the foreign body, or whether the symptoms are psychosomatic in nature. The removal of foreign bodies in a small percentage of cases may be justified on the latter basis after psychiatric consultation.

Summary

A review of the available literature is presented, indicating reasons for the apparent divergence of opinion between surgeons in overseas hospitals and those in the United States towards the removal of intrathoracic foreign bodies.

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MUSCULAR RELAXATION IN ABDOMINAL SURGERY WITH THE USE OF PENTOTHAL-OXYGEN AND CURARE: REPORT OF OVER 600 CASES

Preliminary Report

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Some ten years ago one of us (T.C.D.) helped introduce pentothal-oxygen to the surgical armamentarium of the Georgia Baptist Hospital.[1] This anesthetic agent has been more or less enthusiastically used by the surgeons of Atlanta since that time, but there have been various limitations and objections to the use of pentothal alone which have been based mainly on the large dose of pentothal required for sufficient relaxation. In order to overcome these difficulties and yet to retain the pleasantness and rapidity of induction of pentothal, various surgeons and anesthetists have utilized the synergistic effects of spinal, cyclopropane, nitrous oxide or ether with pentothal-oxygen. However, in spite of the attributes of these methods there have still been objections; so that after the experiences of Griffith, Cullen and others the Anesthetic Department of the Georgia Baptist Hospital tried using curare with pentothal-oxygen in abdominal surgery and the results were so gratifying that this practice has grown in popularity and is now surpassing the other forms of anesthesia used at the Georgia Baptist Hospital.

Curare is not an anesthetic agent, although mild anesthetic properties have been ascribed to it.[2] The main action of curare[9] is muscular relaxation by interrupting the efferent impulses at the myoneural junction, presumably by neutralizing the action of acetylcholine.

The first reference to curare in the literature[3] dates back to Sir Walter Raleigh's account of the discovery of the "large, rich and beautiful empire of Guiana" in 1595. He describes curare's use by the natives in war and hunting and expresses his desire to find an antidote to its poisonous effects.

We find that the first therapeutic use[3] of curare was probably by Demine, who treated 24 cases of tetanus with 8 recoveries circa 1867. Since that time the drug has been variously used for chorea, hydrophobia, fits and tetanus—and by the end of the nineteenth century was recognized in Europe as a therapeutic agent in desperate cases.

After a great deal of experimental investigation in the decade preceding 1940, Bennett[4] first reported its clinical use in preventing

injuries during convulsive seizures in shock therapy in psychiatry. In 1942 Griffith[5] reported its use in anesthesia mainly with cyclopropane and 2 years later Hudon[6] reported its use as an adjunct to pentothal sodium.

Curare is a mixture of the watery extracts of a number of plants mostly of the stychnos species. Its activity is due to the crystalline d-tubocurarine chloride. It is offered for therapeutic use by E. R. Squibb & Sons as "Intocostrin,"[7] a purified and accurately assayed extract from the chondodendron tomentosum.

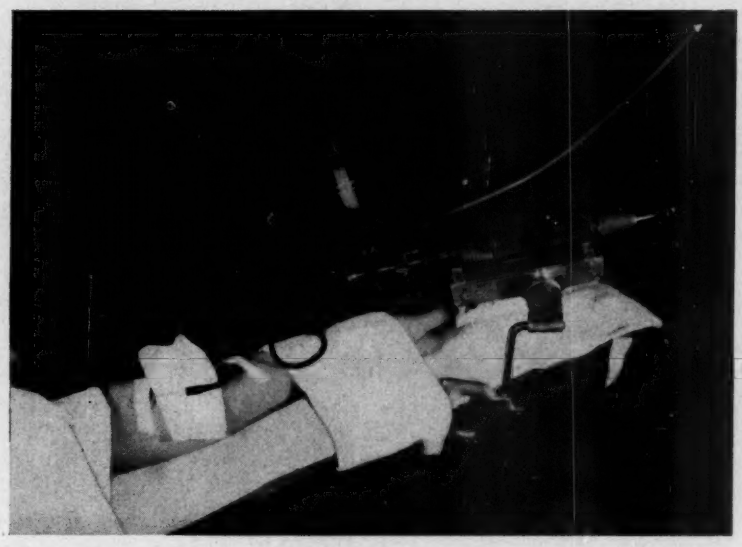
The action of d-tubocurarine chloride,[8] as previously mentioned, neutralizes the acetylcholine reaction at the myoneural junction and can be immediately reversed by physostigmine, which inhibits the choline esterase and restores the acetylcholine preponderance.

Curare affects the various muscles of the body in the following order[9]—first those enervated by the cranial nerves; second those of the trunk and extremities; third those of respiration; fourth and last, those of the diaphragm. There is no effect on the heart action[10] except as might result from apnea and from lowered blood pressure (the latter of which results from peripheral relaxation of the skeletal muscles). The smooth[11] muscles of the vascular system are not affected, nor does the rate, rhythm, P-R, QRS, and QT interval, amplitude or configuration of the individual complexes of the electrocardiogram show any variation. Harris[12] reports that "no changes which at present would be considered abnormal were observed in the electroencephalogram where curare was administered." Griffith[13] states that "curare is rapidly broken down in the body and completely eliminated." The former[10] mostly by the liver and the latter by the kidneys. When curare alone is administered intravenously, it acts within 30 seconds, maintains its maximum effect for 5 to 10 minutes, and then gradually subsides so that the effect is entirely gone in 20 minutes. The rapidity of elimination from the body is undoubtedly the greatest safety factor in the use of curare.

Contraindications[9] to the use of curare are myasthenia gravis and the inability of the anesthetist to perform artificial respiration which can be easily accomplished with a clear air way and an inhalation bag of any anesthetic machine. It is also thought advisable to administer curare rather sparingly to patients suffering liver or kidney deficiency since these organs are instrumental in its detoxification and elimination. A very striking example of an over-dose of curare was reported by Robson[13] of Toronto in 1945. The patient was 2 weeks old, weighed 8 pounds and was being operated on for a complete diaphragmatic hernia. By some mistake she was given

1 c.c. (20 mg.) of intocostrin intravenously, which is some 15 times the recommended dosage for this patient. However, artificial respiration was maintained for more than 3 hours and the baby made a complete recovery.

Method of Administration. (See fig. 1.) Two three-way stopcocks are attached to the syringe on a Rudder Pentothal holder,



and saline, plasma or whole blood (as may be required) is attached to one side. The usual connecting tube leading to the intravenous needle is attached in the usual position. A 2 c.c. syringe is attached to the remaining opening. This 2 c.c. syringe is used to inject intocostrin into the system and can be detached when not in actual use to prevent its falling or being hit and broken off. If intocostrin is injected into pentothal, a yellowish white precipitate is formed which is precipitated barbituric acid and is soluble in an excess of pentothal or plasma.[14] Intocostrin is an organic salt of a weak base and a strong acid, thus is acid in reaction and knocks the basic sodium pentothal out of solution. No harm is done but it is not desirable and may tend to stop up one side of the stopcock. The initial dose of intocostrin is 60 to 80 mg. which is given just after the skin incision is made. More intocostrin is added as needed for desired relaxation, and more pentothal is given as needed to keep the patient lightly anesthetized. Oxygen is given continuously.

OPERATION	PENTOTHAL GRAMS			CURAGE MG.			TIME MINUTES			NO. OF CASES
	Max.	Min.	Av.	Max.	Min.	Av.	Max.	Min.	Av.	
Exploratory	2.5	0.6	1.27	260	80	147.8	110	30	52.9	34
Gall Bladder	2.7	0.7	1.34	200	60	146.0	120	30	70.0	79
Cæsarian Sect.	1.7	1.1	1.43	100	60	80.0	60	40	48.7	6
Intest. & Stom.	3.0	1.2	1.87	300	60	129.0	210	60	124.5	30
Gynecological	3.0	0.8	1.60	260	40	134.3	165	30	80.3	250
Appendectomy	2.5	0.5	1.31	200	40	109.5	75	15	42.5	173
Herniorrhaphy	3.0	0.7	1.87	200	80	125.1	120	40	79.8	37
	Average		1.52	Average		124.5			Total	609

We have compiled the pertinent facts of 609 major operations in which pentothal-oxygen-curare anesthesia was used. For a comparison we also compiled statistics on a corresponding group of cases on which pentothal alone was used, and offer them for your consideration. These cases include our own private patients as well as those of other surgeons of the Georgia Baptist Hospital Staff. This report does not include the many anesthetic agents other than pentothal used with curare whose records are in the archives of the Georgia Baptist Hospital. We would like to pause to say that these anesthesias were quite satisfactory and a definite help was given the anesthetist and surgeon in these cases by the addition of curare and, although no record of the amount of anesthetic agent used is available, it is the opinion of all the anesthetists that considerably less was needed.

The greatest reduction in the amount of pentothal required was observed in the series of exploratory laporotomies. This series included ruptured peptic ulcers, as well as operations where a diagnosis was in doubt and the recesses of the abdomen had to be explored, thus requiring great relaxation of the abdominal musculature. These patients were usually rather excited and had rather severe pain since they were usually emergency operations. The average amount of pentothal required was reduced from 2.12 Gm. to 1.27 Gm., or 40 per cent, by the average addition of 147.8 mg. curare.

The next highest reduction was observed in the series of gall-bladder operations where the pentothal average was reduced from 1.96 Gm. to 1.34, or 31.6 per cent, by the average addition of 146 mg. of curare.

Operation Type	Pentothal—O_2 Alone	Pentothal—O_2 with Curare	Percentage Less Pento.
Exploratory Laparotomy	2.12	1.27	40.0
Gall Bladder	1.96	1.34	31.6
Cæsarian Sect.	1.84	1.43	22.3
Intest. & Stomach	2.33	1.87	19.7
Gynecological	1.90	1.60	15.8
Appendectomy	1.44	1.31	9.0
Herniorrhaphy	1.81	1.87	–3.3
			Av. 19.3

Caesarean section showed the next largest reduction from 1.84 Gm. pentothal to 1.43 with the addition of 80 mg. of curare. We inquired rather closely into this series and found that all the babies breathed immediately—they were all classical Caesarean sections, none being done as the low cervical or the extraperitoneal method so that the time between the injection of the pentothal and curare and the extraction of the child was minimum. There is still some doubt in our minds as to the advisability of doing the other type Caesarean section in which the baby is not as quickly extracted, for it is certainly rational to believe that the baby might receive an overdose of either or both drugs and that difficulty in respiration would follow.

All the stomach and intestinal surgery was grouped together—this included gastrotomy, gastric resections, gastroenterostomies, enterocolostomy, colon resections and colostomies. In the majority of these procedures profound relaxation is mandatory, yet the average was lowered some by the simple operations also included. The average amount of pentothal was reduced from 2.33 Gm. to 1.87 Gm., or 19.7 per cent, with the average addition of 129 mg. curare. These were by far the longest operations of the series, averaging 124.5 minutes, so it is expected that a large quantity of pentothal

would still be necessary to maintain unconsciousness for this period of time. As much as 300 mg. of curare was used on a 47 year old male undergoing gastric resection. This is the largest dose of curare that was given in this series and we would like to point out that this patient had no untoward effects.

Under gynecologic operations were grouped all gradations of pelvic work, from complete hysterectomies to perineal repairs and D & C, so that the average reduction of pentothal is reduced because some of these operations needed little or no relaxation at all and curare was given mainly to broaden our experience with the drug and to prove that it was of relatively little use in operations not needing relaxation. However, the average amount of pentothal was reduced from 1.9 Gm. to 1.6 Gm., or 15.8 per cent.

The average reduction of pentothal used for appendectomies dropped from 1.44 to 1.31, or 9 per cent. This low drop is due to a lessened need for muscular relaxation.

In hernial operations a surprising thing was noted in that the cases using pentothal alone averaged 1.81, while those to whom the curare was also given required 1.87 Gm. pentothal, or an increase of 3.3 per cent. We can only say that this was probably due to the variation in the individual patients of the series. Curare was given these patients as a trial to see how they would react and whether curare could be of any advantage. Apparently it was of no benefit unless some complication arose.

The average reduction of pentothal in the 609 cases here reported varied from 40 per cent to minus 3 per cent, or an average of 19.3 per cent, which is a goodly amount of the drug and was undoubtedly the big factor in reducing the length of postoperative sleeping. In fact the vast majority of these patients were awake by the time the surgeon arrived in the room following the operation.

In some few cases there was a drop in blood pressure, although never over 20 mm. of mercury. This is in accord with the experimental work of Gross, Cullen[15] and with Smith's[16] observations, but in many of these cases there was not any drop in blood pressure and in fact a few showed a slight rise in pressure to which Cullen[17] has also called attention.

There was no instance of phlebitis following curare injection nor any other local effects on the vein.

In spite of all the warnings in every paper we have reviewed concerning respiratory paralysis, there was not a single instance in which artificial respiration was indicated in this series. There was never any need for the injection of prostigmin; however, in a

few cases when our experience with curare was still meager we gave some prostigmin as the patients were leaving the operating table just to assure ourselves that nothing would happen to the patient after returning to the room. But at no time was it really needed.

In administering curare to a patient who is straining and pushing intestines out of the incision, it is an amazing sight to watch those intestines, which were a moment before trying every conceivable trick to escape from the abdominal cavity, now turn and crawl back into the incision. This is thought[15] to be due not to an increased tonicity or activity in the gut but to the improved abdominal muscle relaxation.

It is interesting to note that several cases of hiccough were successfully treated with curare alone after other usual methods had failed.

Conclusions

1. We have reported the use of pentothal-oxygen-curare anesthesia in 609 cases which quite satisfactorily afforded us adequate muscular relaxation under very light anesthesia.

2. We have also reviewed all the available literature about curare.

3. The addition of curare diminished the amount of pentothal used by 19.3 per cent, thus allowing patients to undergo even the largest operations without the attendant dangers of deep anesthesia necessary without curare.

4. We prefer the synergistic effects of pentothal-oxygen-curare in abdominal surgery over spinal, cyclo, nitrous ether or local, either alone or in combination with other agents, including curare, for the induction is rapid, the effects pleasant for the patient—postoperative complications are markedly lowered, the danger of explosion minimized—post spinal headaches, etc., eliminated.

5. Curare should not be used in cases of myasthenia gravis or when the anesthetist cannot give artificial respiration. The inexperienced user of curare should proceed with the utmost caution.

6. We believe that curare is a most valuable adjunct to anesthesia when muscular relaxation is necessary with pentothal or any other anesthetic agent.

We wish to thank the Lending Libraries of the American Medical Association, The American College of Surgeons, the W. F. Prior Co., the E. R. Squibb Co., as well as the Anesthesia Department of the Georgia Baptist Hospital, for their valuable aid in preparing this report.

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AN EVALUATION OF THIOURACIL IN THE TREATMENT OF HYPERTHYROIDISM

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EXCEPT for the continued improvement in technic, the treatment of hyperthyroidism has, during the past several years, changed but little. Because the use of some of the derivatives of thiourea has given hopes that a new and successful method of dealing with hyperthyroidism is now available, and that a substitute for surgery has been discovered, it is timely to evaluate the results of the treatment of thyrotoxicosis by those physicians who have had a very wide experience with these drugs, of which thiouracil and thiobarbital have been the ones most extensively used. Therefore, a questionnaire was sent to each member of the American Association for the Study of Goitre, asking him to relate his experience with this type of treatment.

The membership of this Society is made up of 150 physicians and surgeons in the United States and Canada who have been for many years, and still are, working toward a better understanding of the etiology and treatment of goiter. Most of the individual thyroid specialists, as well as the larger medical and surgical clinics, are represented in this group.

It is therefore fair to assume that if we tabulate and study the results of the treatment of thyrotoxicosis with thiouracil by these physicians, we will have a good overall opinion of its value as it is known at this time.

The physicians replying to the questionnaire reported 1862 patients treated with thiouracil.

The object of this paper is to present to you their results from which six conclusions have been drawn.

With your permission, I shall change the usual method of presentation and state the conclusions first and then discuss each one briefly:

1. Thiouracil plays an important role in effecting a cure for toxic goiter.
2. Thiouracil, without surgery, should not be used as a means of treating toxic goiter, except in carefully selected cases.

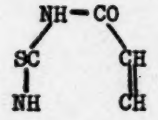
Director of Surgery, St. John's Hospital, and Surgeon in Chief, Carson C. Peck Memorial Hospital, Brooklyn, N. Y.

3. The greatest value of thiouracil is found in the preparation of selected patients, with toxic goiter, for operation.
4. Thiouracil should always be supplemented by the administration of iodine.
5. The use of thiouracil and iodine will eliminate the necessity of multiple-stage operations, and will lessen postoperative morbidity.
6. Thiouracil has in some cases been of value in treating recurrent hyperthyroidism and thyroiditis.

At the present time the mortality of toxic goiter, prepared with iodine, and operated upon by properly trained surgeons, is less than 1 per cent. This mortality rate includes patients who are in extremis due to thyrotoxicosis or who have uncontrollable congestive heart failure, or who have serious complicating diseases, such as diabetes or tuberculosis, or those who develop unpredictable accidents, such as emboli, thrombi, or coronary occlusions.

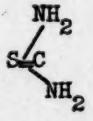
We believe that thiouracil properly used may reduce this present mortality rate.

It is not within the scope of this paper to discuss in detail the pharmacology of thiouracil. For this, it is suggested that reference be made to the numerous articles written on the subject. However, before continuing with the clinical evaluation of the drug, it may be of interest to present its formula and, for comparison, that of sulfadiazine and of thiourea.



2-Thiouracil

Sulfadiazine



Thiourea

In 1945 Hardy, in a paper read before the Passaic County Medical Society, reported that: MacKenzie and Mackenzie[1] in 1941 found that if rats were given sulfaguanidine the thyroid gland increased in size, and at the same time lost some of its colloid.

A little later Kennedy[2] and Richter and Clisby[3] found the same changes in the thyroids in rats that were given thiourea derivatives. A year later the MacKenzies[4] and Astwood[5] at about the same time reported that thiourea and various sulfonamides, when given to rats, acted as thyroid inhibitors and caused hypertrophy of the thyroid gland which was accompanied by a decreased basal metabolic rate.

Subsequently thiouracil was used by various investigators in humans suffering from toxic goiter, and it was found that the thyroid gland enlarged but at the same time the basal metabolic rate decreased and many of the thyrotoxic symptoms subsided.

Thiouracil in some way slows the synthesis of thyroxin and thereby acts as a thyroid inhibitor.

A study of sections of thyroid glands after treatment with this drug demonstrated that the colloid within the acini was decreased. This resulted in the stimulation of the anterior pituitary gland and caused the release of a thyroid-stimulating hormone which, in turn, produced marked hyperplasia of the thyroid, and which was manifested clinically by an enlarged and softened gland.

The Clinical Use of Thiouracil

Various clinicians of equal ability have published conflicting reports concerning the efficiency of thiouracil without surgery as a cure for thyrotoxicosis. It is my belief that many of the articles reporting successful results were colored by the enthusiasm of observers who arrived at their conclusions before a sufficient number of cases had been treated, and before sufficient time had elapsed to know that a cure had been effected.

If we analyze the experience of the members of the American Association for the Study of Goitre, answering the questions "Have you used thiouracil without surgery as a method of treating hyperthyroidism?" and "What has been the percentage of good, fair, and unsatisfactory results?" we find that approximately 40 per cent of the physicians replying had used it in 708 cases, and that the other 60 per cent had used it only for preparing the patient for operation.

In other words, thiouracil has been given a fair trial in a goodly number of cases by a relatively large group of careful observers, so that valuable conclusions can be drawn from the reported results.

However, it is interesting to note that there were 10 physicians who obtained 50 or more per cent satisfactory results, and 19 physicians who obtained 50 or less per cent unsatisfactory results.

Attention is called to the third and sixteenth lines* of Table I.

TABLE I

CASES TREATED WITH THIOURACIL WITHOUT SURGERY

No. of Cases	*Good Results*	*Fair Results*	*Unsatisfactory Results*
12	100	—	—
6	90	?	?
*20	90	9	1
53	90	?	?
35	88	6	6
40	60	30	10
2	50	—	50
35	50	20	30
45	50	30	20
35	50	20	30
60	20	10	70
15	—	60	—
14	21	58	21
40	15	30	55
10	4	70	26
*25	2	—	98
?	—	2	3
12	?	?	?
21	0	0	100
4	0	0	100
3	—	+	—
32	—	+	—
30	—	+	—
11	—	—	+
11	—	—	+
51	—	—	100
4	—	—	100
12	—	—	100

Dr. A. used thiouracil in 25 cases with 2 per cent satisfactory results, and Dr. B used it in 20 cases with 90 per cent satisfactory results. One explanation of this discrepancy probably lies in the fact that the two groups of patients were not at all comparable.

If Dr. A. were presenting this paper, he would undoubtedly tell us that thiouracil was of no value as a cure for hyperthyroidism whereas Dr. B. would be equally emphatic that it was the method of choice. It is evident therefore that the proper selection of cases for treatment is of paramount importance and that a large number of cases be studied before arriving at conclusions. No rule of thumb can be used concerning the indications for its administration. No tests will replace the judgment of physicians trained in the management of thyroid disease; a judgment which is acquired only after

years of experience. We know that there are many cases of toxic goiter in which surgery is for some reason contraindicated. We know that some of these patients have responded satisfactorily to thiouracil and that if properly used it can be continued for a relatively long period. We also know that it has been possible to discontinue the drug and that a few patients have remained in a satisfactory state of metabolic balance for considerable periods of time.

CHART 1

THIOURACIL WITHOUT SURGERY

NUMBER OF DOCTORS	CASES WITH LESS THAN 50% GOOD RESULTS	NUMBER OF DOCTORS	CASES WITH MORE THAN 50% GOOD RESULTS	NUMBER OF DOCTORS	CASES WITH 50% GOOD RESULTS
19	475	6	116	4	117

As is shown in Chart 1, 19 physicians treated 475 patients with unsatisfactory results. Six physicians treated 116 patients with what they considered to be good results, whereas 4 physicians treated 117 patients with what they considered to be only fair results. This experience demonstrates that in the hands of these particular physicians the use of thiouracil as the sole means of curing hyperthyroidism was unsuccessful.

There are, however, some very definite indications for its use in the cure of goiter. Occasionally a severely toxic patient will refuse surgery. There may be some serious associated diseases such as tuberculosis, diabetes, acute congestive heart failure with auricular fibrillation so pronounced that surgery would be contraindicated. There is also a group of patients who do not respond to iodine.

CHART 2

Complications	Occasional Cases Reported
Number of Cases	
40—Skin	Headache
32—Leucopenia	Myasthenia
22—Agranulocytosis	Edema
16—Vomiting	Painful Joints
14—Nausea	Neutropenia
14—Fever	Dental Abscess
10—Severe "OP" Bleeding	General Malaise
10—Swollen Lymph Nodes	
6—Muscle Pains	
6—Swollen Salivary Glands	
3—Acute Hepatitis	

These patients should certainly be treated with thiouracil. Even though its use does not result in a cure, there may be sufficient improvement, which could not be obtained with iodine, so that surgery can be done safely.

It is interesting to note that there was not a single physician who found that any patient had become thiouracil-fast.

Complications

It must be emphasized that thiouracil, like most valuable drugs, is a dangerous one unless it is carefully controlled.

Even during the experimental years, when it was not available to the general medical profession, and when it was administered by cautious observers, many complications arose.

The following is an analysis of its results in 513 cases as reported by Hardy during this period.

Fortunately, most of the untoward sequelae such as skin reactions, vomiting, nausea, swollen lymph nodes, fever, headache, edema, swollen and painful joints, and malaise are transient, are not very serious, and disappear after the drug is discontinued.

However, there is a very real percentage of cases in which extremely disastrous complications have developed, namely, agranulocytosis, neutropenia, leucopenia and acute yellow atrophy of the liver.

In January, 1946, thiouracil was placed on the market, and became available for prescription use.

One of the objects of presenting this paper is to caution against

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PEARL RIVER, NEW YORK

AN ANALYSIS OF 513 DERACIL-TREATED PATIENTS, NOT PREVIOUSLY REPORTED OR INCLUDED IN FIRST F.D.A. APPLICATION

(Taken from case reports sent in by physicians who have been using Deracil for clinical investigation)

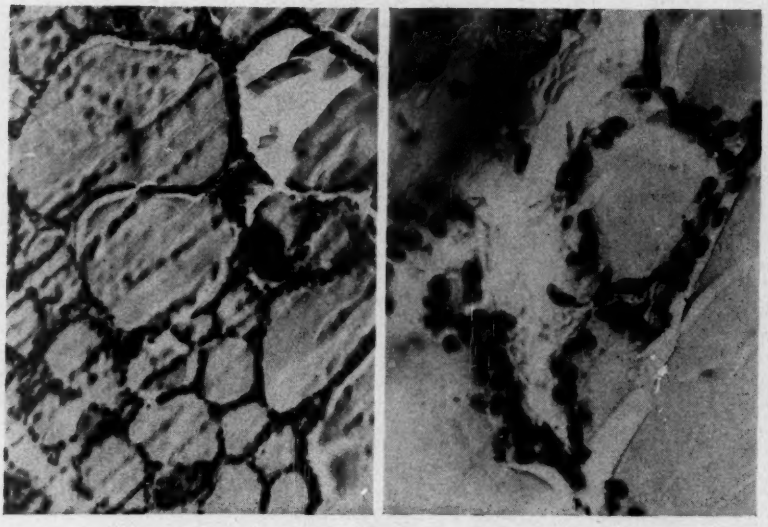
	No. Cases	*Per Cent Total*
Total number of Deracil-treated patients in series	513	
Results of treatment:		
Improved	433	84.40
Unimproved	73	14.23
Died	7	1.37
Death due to toxicity of Deracil	4	0.78
Death from other causes (cardiac, etc.)	3	0.59
Number of patients showing toxic side reactions to Deracil	104	20.27
Number of cases in which drug had to be discontinued because of toxic side reactions to Deracil	52	10.14
Types and frequency of toxic reactions to Deracil:		
1. Leucopenia	32	6.23
2. Nausea and/or vomiting	19	3.70
3. Hyperpyrexia	17	3.50
4. Dermatitis	15	2.92
5. Agranulocytosis	10	1.94
6. Oruritis	8	1.55
7. Headache	7	1.37
8. Vertigo	6	1.11
9. Jaundice—liver damage	5	0.97
10. Adenitis	4	0.78
11. Diarrhea	3	0.58
12. Joint pains	2	0.39
13. Anemia (not associated with agranulocytosis)	1	0.19
Causes of death of Deracil-treated cases:		
Not attributed to Deracil toxicity:		
Postoperative pneumonia	1	
Cardiac failure	2	
Death attributed to toxicity from Deracil:		
*Agranulocytosis	3	
**Acute yellow atrophy of the liver	1	

*Other fatalities from agranulocytosis have been published in the literature or informally reported to us, and are not included in this series.

**At least one other fatality due to liver atrophy has been reported.

its administration without proper control and to sound a warning concerning its dangers.

Because of my personal experience, together with that of others, I am convinced that, as a general rule, a patient who is sufficiently



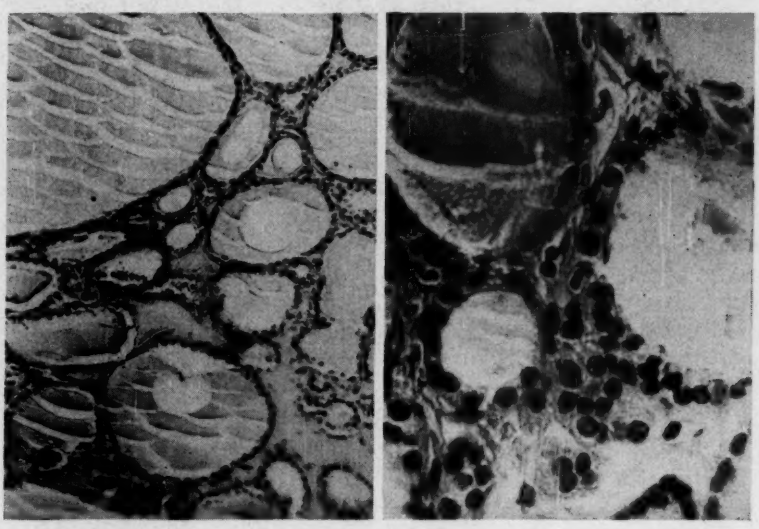
A B

Fig. 1. Photomicrographs (Normal Thyroid)

Cells are relatively flattened with a non-vacuolized, fairly deep staining material in the follicle. The colloid in this *normal thyroid* doesn't seem to have as much crenation at the edges where it connects with the epithelial cell as it does in the abnormal thyroid. There is a large percentage of pyknotic nuclei in small dark cells, the so-called colloid cells of Langendorff. These degenerating cells seem to have some correlation with inactivity, or at least the lack of abnormal activity, of the thyrotoxic gland. The Golgi apparatus seems to be somewhat decreased in amount and a mitochondria of about normal. This slide therefore shows the stage of colloid absorption and transport rather than an active secretory process.

toxic to require this drug, is sick enough to require hospitalization. There are of course exceptions to this. If a patient is situated so that he can have daily blood counts, and competent nursing care, and so that the early symptoms of thiouracil toxocity can be reported, the drug may be administered at home. However, complications may develop very quickly, within a few hours, and may be very serious unless prompt treatment is instituted. One of the major complications is acute yellow atrophy of the liver, manifested by jaundice and abnormal sulfobromophthalein retention. We have found 18 such cases reported. However, the most critical complication is the development of agranulocytosis. It is important to re-

member that frequently a sore throat, backache, and headache, are the first signs of this condition, and may appear before any blood changes are found. It is, therefore, important to caution the house officers, nurses, and the patients themselves to be on the lookout



A B

Fig. 2. Photomicrographs (Thyrotoxicosis untreated)

The thyrotoxic gland exhibits less uniformity of size of the follicles than the normal. The colloid is somewhat lighter in color, has crenated edges, has moderate vacuolization indicative of abnormally increased colloid activity. The cells are higher tending towards a high cuboidal; mitochondria are decreased and Golgi apparatus seems more evident. This latter finding is suggestive of active formation of secretion. Some invagination of the epithelial cells into the ascini can be seen along with several abnormally sized follicles which are much larger than the largest of those in the slide of the normal thyroid, using the same magnification and even the same microscope for comparison. Many ascini have had such an extreme degree of vacuolization and absorption that only a part of the ascini shows markedly depleted to almost no colloid at all. There are more clear celled epithelial elements in this thyrotoxic patient's slide, suggesting increased hypertrophy and hyperplasia.

for, and to report, these symptoms which are quite similar to those which usher in so-called grippe. The drug should be stopped at once. Penicillin should be given in appropriate doses, usually 30,000 to 40,000 units every 3 hours, as long as indicated. This will frequently check the complications due to infection until the blood count has been restored to normal. Many other preparations have been suggested and tried, including crude liver extract, pyridoxine, pantothenic acid, folic acid, vitamins and pentanucleotide, but, to date, penicillin has given by far the most satisfactory results. Con-

sidering this group as a whole, about 10 per cent, or one out of every 10 patients, developed complications which made withdrawal of the drug mandatory. Approximately 3 per cent developed agran-

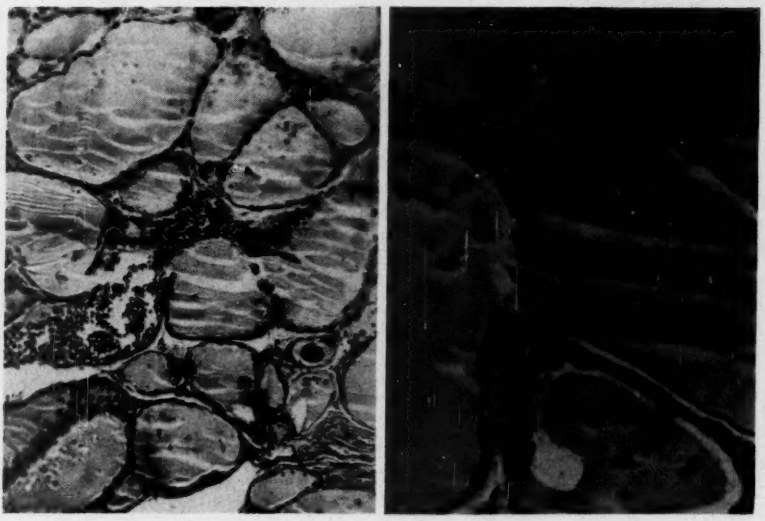


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Fig. 3. Photomicrographs (Thyrotoxicosis treated with thiouracil only)

Thyrotoxicosis treated with thyouracil only and then operation. Here the action of thiouracil is quite interesting. A disorganization of the pattern of the thyroid gland becomes evident. Disparity in size from extraordinarily large ascini to extremely small infant ascini is readily apparent. The breakdown of the follicle, with tendency of several to coalesce, and the increased colloid absorption visible in these slides suggest that this is one way in which colloid absorption obtains. Increased vacuolization with even vacuoles in the epithelial cells themselves is also part of this process. The cells are more pyknotic in character with dark nuclei than in an untreated thyrotoxicosis. Their size is less as they tend to be lower in height, cuboidal rather than the now columnar of the previous slide, that of thyrotoxicosis. Mitochondria seem to be slightly increased.

ulocytosis. The death rate, in spite of intensive treatment, in this group was 26 per cent.

Several of the deaths occurred in patients who received sulfonomides, in addition to thiouracil. In view of the fact that both of these drugs tend to depress the leucocytes, we believe they should never be used concomitantly. Because of these untoward reactions, and because the treatment must be continued over a long period of time, during which serious complications may develop, even though frequent check-ups are made, and because surgery has given such satisfactory results, we believe that in the vast majority of cases, the latter is the treatment of choice.

It must be remembered that a great deal of thyroid surgery is done outside of the metropolitan areas. One surgeon writes as follows: "One thing has been left out of the papers appearing in the journals concerning the use of thiouracil, and that is, the condition under which a surgeon has to prepare his patients for operation. In my own case, over 90 per cent of the goiter cases I see come from outside of my city, from different points in this state and surrounding states. Many of these patients cannot afford to stay in the hospital, and many of them are separated from their family physician by long distances. Because of these facts, it would be impossible for me to use this drug safely in treating most of my patients."

However, as a result of our own experience, and after analyzing the results of the use of thiouracil in nearly 2,000 compiled cases, we believe that it is of great value in preparing selected patients for operation. We believe, nevertheless, that its routine preoperative use in the average case of thyrotoxitosis is not necessary. For many years experience has proven that patients with severe thyrotoxicosis having metabolic rates of 40 per cent or 50 per cent or more can be satisfactorily prepared for surgery with iodine in about 3 to 4 weeks. A part of this preparatory period may be safely spent at home. Whereas if thiouracil is used, much more time will be required, and there is the probability that 10 per cent of these patients will develop complications which will make it necessary to withdraw the drug, and that about 2 per cent may be fatal.

However, if thiouracil is well tolerated, it will almost invariably bring the basal metabolic rate to normal, at the rate of 1 degree per day. Whereas with iodine it is frequently impossible to reduce the rate below 20 or 30. Experience in thousands of cases thus far has shown that when thiouracil is used, the postoperative crises are less common, the postoperative temperature is lower, the postoperative morbidity is decreased, and the necessity for multiple stage operations has been eliminated.

We believe, therefore, that thiouracil should be used in preparing severely thyrotoxic patients for surgery, patients in whom our experience in the past has taught us that a multiple stage operation would have to be done if iodine were used, and in whom our experience has also shown that iodine would probably not reduce the basal metabolic rate to a safe level. As stated above, no rule of thumb can be given concerning the selection of cases. The decision as to whether thiouracil should or should not be used rests with the surgeon. No test will replace surgical judgment.

Earlier in the paper we described the hyperplasia, the softening,

the increased vascularity, and the lack of involution found in the thyroid gland treated with thiouracil. If operation is done when there is no involution of the gland, distressing technical difficulties are encountered. The gland bleeds profusely. The clamps bite

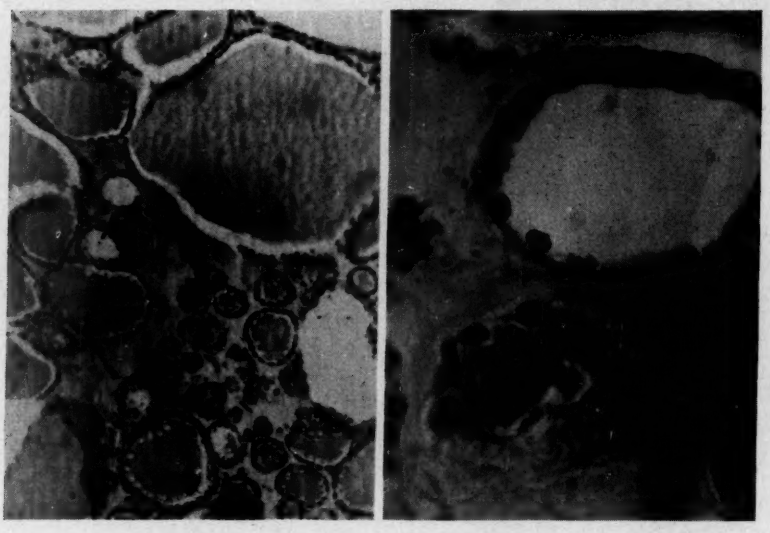

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Fig. 4. Photomicrographs (Thyrotoxicosis treated with thiouracil and iodine combined treatment)

Thyrotoxicosis treated with thiouracil and iodine (combined treatment), and then operation. The disorganized pattern in the thiouracil effect is again visualized here. The height of the cells, however, is much reduced in size, tending towards the flattening seen in the resting stage of the normal thyroid. There is an increased evidence of breakdown in the unity of individual follicles which is visible extremely well in the high-powered slide. Increased fibrosis, some increase in colloid obtains. Mitochondria are not as common or as frequent as in the previous slide. Here can be seen in the colloid material (under high power) the breakdown of the colloid cells of Langendorff.

through the tissue. The sutures and ligatures do not hold, and frequently the operation has to be terminated, and the wound packed. If, however, iodine is properly administered, involution does occur. The gland becomes firm, and it presents no such technical problems. It is now generally agreed that the proper administration of iodine is as follows:

> Give Lugol's solution during the last 3 weeks of preparation. Stop thiouracil one week before the operation, but continue the use of Lugol's solution during this last week.

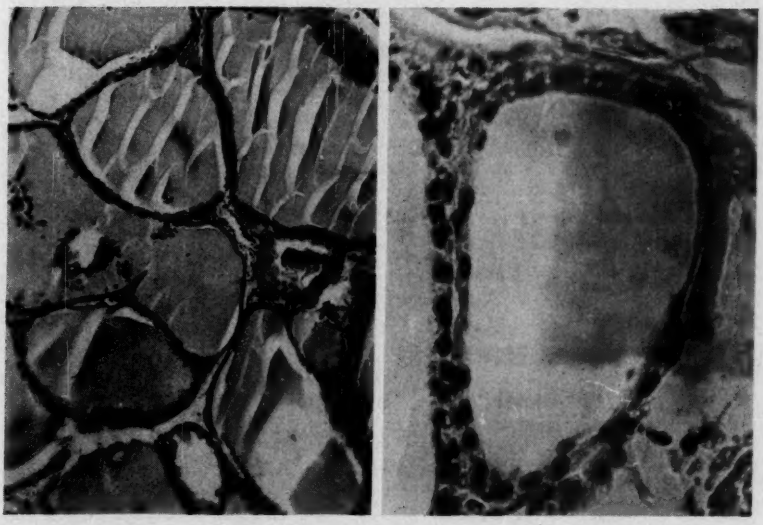

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Fig. 5. Photomicrograph (Thyrotoxicosis treated with iodine only)

Thyrotoxicosis treated with iodine only and then operation. **The cells here are flattened, are much more pyknotic in nuclei formation and in their staining properties. Mitochondria are increased as is also the formation of the Golgi bodies. This suggests a balance between secretion and absorption, Vacuolization is present but much less than in the previous slide. The impression is that here the therapy of iodine has tended to produce an attempt on the part of a thyrotoxic gland to return to some degree of microscopic normalcy. It is worthwhile remembering that increased formation of secretion of colloid finds an increase in the Golgi bodies and a decrease in the mitochondria. With increased absorption of the colloid or its depletion from the thyroid gland the reverse obtains and here the Golgi bodies decrease in quantity and the mitochondria increase. In other words, with the increase in both, the evidence suggests that thiouracil and iodine affect respectively the mitochondria and the Golgi bodies. The observation at this point must be made that the microscopic picture of the thyroid gland is changed under the influence of hyperplasia and hypertrophy. In thyrotoxicosis not only are the glandular elements changed in quantity and character but also the great probability is that some qualitative change in the thyrotoxic hormone obtains. Microscopically, though, it may be said that thiouracil, either by itself or with iodine, tends to disrupt the normal pattern of the gland, thereby reducing its efficiency and thus mitigating the extent and degree of secretion and absorption of thyroxin. This has been evaluated in the above and by means of graphic demonstrations the qualitative and quantitative changes in the glandular physiology under the influence of thiouracil will now be demonstrated.**

In other words, if the basal metabolic rate was plus 60 at the beginning of the preparatory period, it will return to normal in about 60 days. Start thiouracil .2 Gm. t.i.d. On the 39th day add Lugol's solution, minims 10 t.i.d. On the 53rd day stop thiouracil but continue the Lugol's solution during the next 7 days before operation.

If thiouracil fails to control the toxicity, and the patient is known

to be a poor operative risk, thiobarbital may be tried. This is a more potent drug, and the dose should be about .2 Gm. per day. Even if thiobarbital is administered, iodine should always be given during the last 3 weeks, in exactly the same manner as when thiouracil is used.

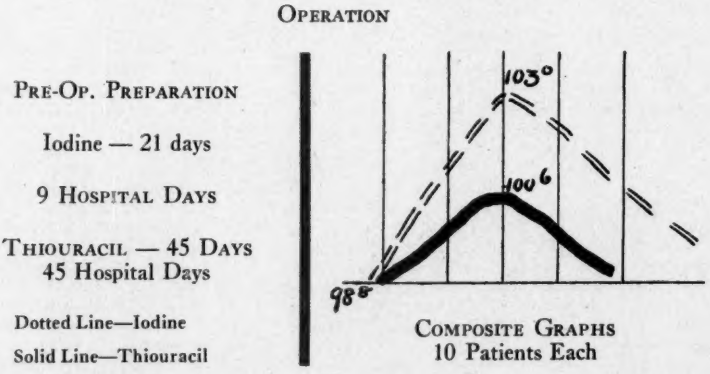
It was found that thiobarbital caused about the same types of complications as did thiouracil but they occurred nearly 3 times as frequently.

We have observed that occasionally patients on this regime develop a very low basal metabolic rate, and that myxedema followed. If this does occur, sufficient thyroid extract should be used to bring the basal metabolic rate to normal before doing surgery.

It is interesting to note that out of all those who replied to the questionnaire, only two surgeons reported severe crises following the use of thiouracil.

The accompanying graph shows the difference between two groups of 10 patients each having approximately the same types of glands, and approximately the same degree of thyrotoxicosis before operation.

POSTOPERATIVE TEMPERATURES



The lack of high postoperative temperature and pulse rate is striking in the latter group. In the past the postoperative crises which developed in patients prepared with iodine could usually be controlled by sodium iodide, transfusions, intravenous fluids, and oxygen, but the patients prepared with thiouracil and iodine have been spared many distressing days of postoperative reactions and acute illness. The surgeon and his staff have been spared an equal

number of days of worry and anxiety while waiting for these crises to pass.

The use of thiouracil should be considered, and may be of great value in handling severe thyrotoxicosis, occasionally seen during the later months of pregnancy.

It is true that iodine controls the toxic manifestations in these patients in about 3 weeks. This is, however, much earlier than is desired because it necessitates surgery being done before delivery or very shortly thereafter.

If thiouracil is well tolerated the thyrotoxicosis can be controlled and, by gradually reducing the daily amount to a maintenance dose of .1 Gm. or .2 Gm. a day, the patient can be carried along for several months until such time as the operation can be done electively.

It was mentioned earlier in the paper that surgical resection is occasionally followed by a recurrence, or perhaps a persistence, of hyperthyroidism associated by varying degrees of thyroid hyperplasia.

Twenty-four surgeons stated that they had used thiouracil in these cases of so-called recurrent hyperthyroidism. The physicians from the larger clinics reported that their results had been very unsatisfactory—stating that the disease recurred after the drug was discontinued.

Our experience, as well as that of other individual observers, has led us to believe that if there is a gross recurrence of the gland tissue, surgery is indicated. If, however, thyrotoxic symptoms develop, with little or no demonstrable gland hyperplasia, thiouracil may be tried. But if the symptoms persist, resection should be done promptly.

True thyroiditis is a disease so relatively rare that very few cases treated with thiouracil were reported. It is generally felt, however, that it should be tried in this condition, because most of the cases in which it was used did not go on to suppuration. Whether these would have suppurated if the drug had not been used is not known. Many more cases will have to be treated before any worthwhile evaluation can be given as to its effectiveness in this disease.

Summary

1. Out of the 1862 cases of toxic goiter reported, 708 were treated with thiouracil in the hope that surgery would not have to be done. Out of these 708 cases, 116 were reported by 5 physicians as having obtained "good results." In 12 of these cases 100 per

cent "satisfactory results" were recorded. In the remaining 592 cases, however, "unsatisfactory results" were obtained. In 90 of these, 100 per cent "failures" were reported.

It is concluded, therefore, that the treatment of hyperthyroidism by thiouracil has been thus far unsatisfactory.

2. Thiouracil has been found to be of great value in preparing properly selected cases for operation, namely, those in which multiple stage operations would have to be done, those with very severe thyrotoxicosis, having excessively high basal metabolic rates, those having severe congestive heart failure or suffering from severe complicating diseases and those who have become iodine-resistant.

3. No patient treated with thiouracil should be subjected to surgery without the proper administration of iodine during the last 3 weeks of preparation.

4. The value of thiouracil in so-called recurrent hyperthyroidism and acute thyroiditis is still questionable.

The author wishes to express his appreciation to the members of the American Association for the Study of Goitre who replied to the questionnaire and who, by so doing, made the preparation of this paper possible. He is also indebted to Dr. Stanton M. Hardy, Medical Director of the Lederle Laboratories, for the analysis of 513 cases collected by him; and to Dr. Martin Ratzan for the preparation and study of the photomicropraphs.

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RECENT ADVANCES IN SURGERY

The most dramatic reflection of the great advances in surgery which have taken place in the last few years are shown in the astonishingly good results obtained with those wounded in combat during the last war. According to Surgeon General Norman T. Kirk, 598,000 soldiers were wounded during the war and approximately 96 per cent of those who reached army hospitals lived. This was due in large part to the immediate surgical treatment which they received at the front lines.

Three major methods were responsible for these excellent results. For the first time front line soldiers wounded in this war received plasma almost at once. This alone was responsible for having saved many lives. Also, the sulfa preparations were given promptly after wounding, thus preventing a great many infections which would formerly have resulted in death. At the front line, too, more prompt control of hemorrhage was employed than ever before. All these are aids to surgery which will be applicable in much civilian work.

The treatment of burns—a surgical problem—has been greatly improved. In part this is due to the use of plasma, salt solution, and whole blood. In part also new methods of local treatment have been devised which have greatly improved the chance of recovery. The chief difficulty here is that so many methods have been suggested that it is hard to choose.

During the past few years several technical aids to surgery have been developed. There are several new hemostatic agents, including fibrin foam, gelatin sponges and oxide cellulose, which make the control of bleeding during and after an operation much more successful. These substances probably will be particularly helpful in special fields of surgery involving vascular areas such as around the brain, where control of hemorrhage is especially difficult. New dressings for wounds, such as the surgical rayons and new and improved surgical sutures, can be used with advantage in many operations.

In abdominal surgery, the method of intestinal decompression is of great help both before operation and afterward. Preoperatively, intestinal decompression helps in preparing the patients. Postoperatively, the decompression apparatus helps to protect the sutures from being torn out as well as to increase the comfort of the patient. The Whipple operation and its modifications for cancer of the biliary tract has meant that operations can be carried out which could not even be considered before.

New technics have been developed in special fields of surgery at a rate which is little short of amazing. The methods of skin grafting have been greatly improved as have other technics in plastic surgery. Nerve repairs can now be made, as well as other forms of neurosurgery which were impossible only a few years ago. Operations on and in the thoracic cavity have been greatly advanced. The shunting of the blood back to normal channels by means of some of the new methods of heart surgery is another example of development of ingenious new surgical technics. The operation of lumbodorsal sympathectomy for some patients with hypertension has great promise, but it, like many of the other highly developed surgical technics, is not one on which the general surgeon can embark lightly.

Although, in developing new technics, surgeons have at least kept pace if not exceeded all other fields of medicine, it is in the treatment of surgical shock, the early prevention of infection, and in postoperative care that the outlook for surgical patients has been most improved. There is little need to worry any more about tetanus. Patients, even those who are in bad general shape, can be prepared for operation in a way which makes their chances of coming through far better than ever before.

One of the paramount advances in the prophylactic and therapeutic treatment of infections has been the use of penicillin. This agent has proved effective in arresting and retarding the growth of micro-organisms which previously have been resistant to other drugs

and often fatal because of overwhelming infections and toxicity. Another drug which gives promise of becoming a great aid in infections where thus far penicillin and other drugs have failed is streptomycin. However, the true value of streptomycin in surgery remains yet to be proved.

As has been true of all wars of recent centuries, the new technics discovered will be applicable to civilians and will be used to save many lives during the peaceful years ahead.

E. L. HENDERSON.

UNIVERSITY NUMBERS OF THE SOUTHERN SURGEON

In an effort to cooperate more closely with the medical colleges throughout the Southeastern States, the Executive Council of The Southeastern Surgical Congress has recommended that at least two issues of THE SOUTHERN SURGEON be devoted entirely to the Medical Departments of these universities. If this recommendation meets with a ready response from the universities, four issues may be devoted to this program. Already two universities have expressed a desire to utilize the journal and a program from one has already been completed for the second number to be published in 1947. Under our present arrangement, the Medical Department of the University of Alabama will utilize the entire February issue and the August issue will be devoted to the Medical Department of the University of Tennessee.

During the year 1947 all the medical colleges in this territory will be invited to participate in this undertaking. The exact order in which the numbers will be allocated has not been determined by the Council.

The Council feels that this is a timely step forward in carrying out one of the purposes for which The Southeastern Surgical Congress was organized more than fifteen years ago.

Mg. Ed.

Urology Award. The American Urological Association offers an annual award, not to exceed $500, for an essay (or essays) on the result of some clinical or laboratory research in Urology. Competition shall be limited to urologists who have been in such specific practice for not more than five years and to residents in urology in recognized hospitals.

For full particulars, write the Secretary, Dr. Thomas D. Moore, 899 Madison Avenue, Memphis, Tennessee. Essays must be in his hands before May 1, 1947.

The selected essay (or essays) will appear on the program of a forthcoming meeting of the American Urological Association, to be held at the Hotel Statler, Buffalo, New York, June 30-July 3, 1947.

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